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Piot-Grosjean et al.

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(54) **COMBINATION OF A CB1 RECEPTOR ANTAGONIST AND OF SIBUTRAMINE, THE PHARMACEUTICAL COMPOSITIONS COMPRISING THEM AND THEIR USE IN THE TREATMENT OF OBESITY**

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A61K 31/397 (2006.01)

(52) **U.S. Cl.** **514/646**; 514/210.01

(58) **Field of Classification Search** 514/646, 514/210.01, 210.19, 210.2, 210.21

See application file for complete search history.

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(57) **ABSTRACT**

The present invention relates to the combination of a CB1 receptor antagonist and of sibutramine, to the pharmaceutical compositions comprising them and to their use in the treatment of obesity.

11 Claims, No Drawings

1

**COMBINATION OF A CB1 RECEPTOR
ANTAGONIST AND OF SIBUTRAMINE, THE
PHARMACEUTICAL COMPOSITIONS
COMPRISING THEM AND THEIR USE IN
THE TREATMENT OF OBESITY**

The present invention relates to the combination of a CB1 receptor antagonist and of sibutramine, to the pharmaceutical compositions comprising them and to their use in the treatment of obesity.

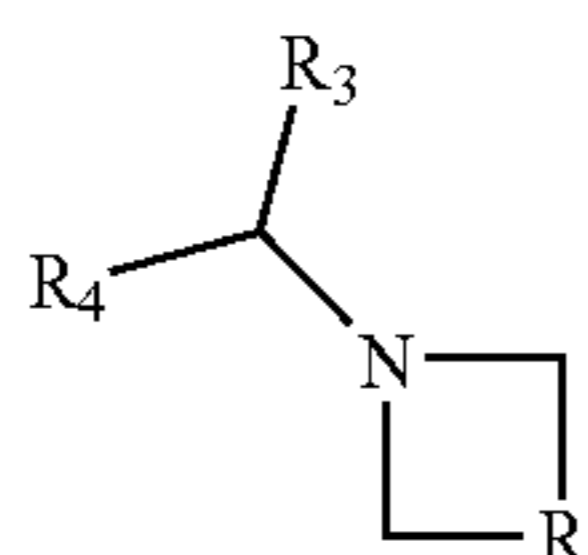
CB1 receptor antagonists are known for their effect on food intake and their use as anorexigenic (G. Colombo et al., *Life Sciences*, 63 (8), 113–117 (1998); J. Siamand et al., *Behavioural Pharmacol.*, 9, 179–181 (1998)).

Sibutramine (BTS 54524; N-{1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutyl}-N,N-dimethylamine; Meridia®, Reductil®), its hydrate and its pharmaceutically acceptable salts and in particular its hydrochloride reduces food intake and is of use in the treatment of obesity (WO 90/061110; D. H. Ryan et al., *Obesity Research*, 3 (4), 553 (1995); H. C. Jackson et al., *British Journal of Pharmacology*, 121, 1758 (1997); G. Fanghanel et al., *Inter. J. Obes.*, 24 (2), 144 (2000); G. A. Bray et al., *Obes. Res.*, 7 (2), 189 (1999)).

It has now been found that the combination of sibutramine, its hydrate and its pharmaceutically acceptable salts and of a CB1 receptor antagonist exhibits a synergistic effect in reducing food consumption and is thus of use in the treatment of obesity.

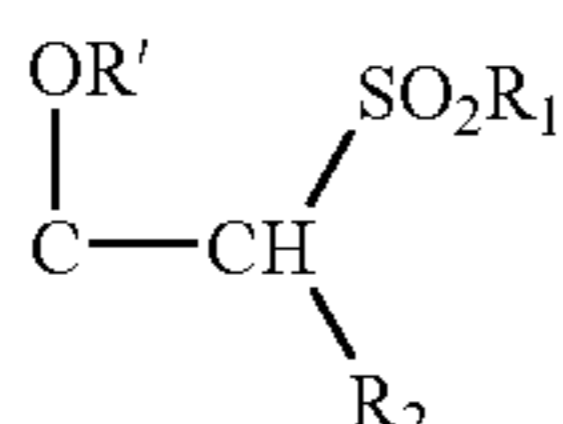
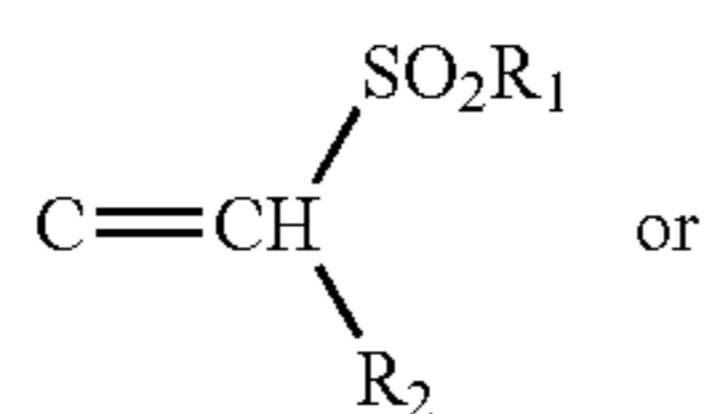
The combination can also comprise several CB1 receptor antagonists.

Use may in particular be made, among CB1 receptor antagonists, of the azetidines disclosed in WO 00/15609, WO 01/64633 and WO 01/64634 of formula:



in which

either R represents a chain (A) or (B) and



R₁ represents a methyl or ethyl radical,

R₂ represents either an aromatic chosen from phenyl, naphthyl or indenyl, these aromatics being unsubstituted or substituted by one or more halogen, alkyl, alkoxy, —COalk, hydroxyl, —COOR₅, formyl, trifluoromethyl, trifluoromethylsulfanyl, trifluoromethoxy, nitro, —NR₆R₇, —CO—NH—NR₆R₇, —N(alk)COOR₈, cyano, —CONHR₉, —CO—NR₁₀R₁₁, alkylsulfanyl, hydroxyalkyl, —O-alk-NR₁₂R₁₃ or alkylthioalkyl, or a heteroaromatic chosen from the benzofuryl, benzothiazolyl, benzothienyl, benzoxazolyl, chromanyl, 2,3-dihydrobenzofuryl, 2,3-dihydrobenzothienyl, indolyl, indolyl, isochromanyl, isoquinolyl, pyridyl, quinolyl, 1,2,3,4-tetrahydroisoquinolyl, 1,2,3,4-tetrahydroquinolyl, thiazolyl or thienyl rings, it being possible for these heteroaromatics to be unsubstituted or substituted by a halogen, alkyl, alkoxy, —COOR₅, trifluoromethyl, trifluoromethylsulfanyl, trifluoromethoxy, nitro, —NR₆R₇, —CO—NH—NR₆R₇, cyano, —CONHR₉, alkylsulfanyl, hydroxyalkyl or alkylthioalkyl,

2

matic chosen from the benzofuryl, benzothiazolyl, benzothienyl, benzoxazolyl, chromanyl, 2,3-dihydrobenzofuryl, 2,3-dihydrobenzothienyl, indolyl, indolyl, isochromanyl, isoquinolyl, pyridyl, quinolyl, 1,2,3,4-tetrahydroisoquinolyl, 1,2,3,4-tetrahydroquinolyl, thiazolyl or thienyl rings, it being possible for these heteroaromatics to be unsubstituted or substituted by a halogen, alkyl, alkoxy, —COOR₅, trifluoromethyl, trifluoromethylsulfanyl, trifluoromethoxy, nitro, —NR₆R₇, —CO—NH—NR₆R₇, cyano, —CONHR₉, alkylsulfanyl, hydroxyalkyl or alkylthioalkyl,

R₃ and R₄, which are identical or different, represent either an aromatic chosen from phenyl, naphthyl or indenyl, these aromatics being unsubstituted or substituted by one or more halogen, alkyl, alkoxy, formyl, hydroxyl, trifluoromethyl, trifluoromethoxy, —CO-alk, cyano, —COOR₅, —CONR₁₀R₁₁, —CO—NH—NR₆R₇, alkylsulfanyl, hydroxyalkyl, -alk-NR₆R₇ or alkylthioalkyl, or a heteroaromatic chosen from the benzofuryl, benzothiazolyl, benzothienyl, benzoxazolyl, chromanyl, 2,3-dihydrobenzofuryl, 2,3-dihydrobenzothienyl, furyl, isochromanyl, isoquinolyl, pyrrolyl, quinolyl, 1,2,3,4-tetrahydroisoquinolyl, thiazolyl or thienyl rings, it being possible for these heteroaromatics to be unsubstituted or substituted by a halogen, alkyl, alkoxy, hydroxyl, trifluoromethyl, trifluoromethoxy, cyano, —COOR₅, —CO—NH—NR₆R₇, —CONR₁₀R₁₁, -alk-NR₆R₇, alkylsulfanyl, hydroxyalkyl or alkylthioalkyl,

R₅ is an alkyl radical or a phenyl radical optionally substituted by one or more halogen atoms,

R₆ and R₇, which are identical or different, represent a hydrogen atom or an alkyl, —COOalk, cycloalkyl, alkylcycloalkyl, -alk-O-alk or hydroxyalkyl radical or else R₆ and R₇ form, together with the nitrogen atom to which they are attached, a saturated or unsaturated and mono- or bicyclic heterocycle having 3 to 10 ring members optionally comprising another heteroatom chosen from oxygen, sulfur and nitrogen and optionally being substituted by one or more alkyl, —COalk, —COOalk, —CO—NHalk, —CS—NHalk, —CO-alk-NR₁₄R₁₅, oxo, hydroxyalkyl, -alk-O-alk or —CO—NH₂ radicals,

R₈ represents an alkyl radical,

R₉ represents a hydrogen atom or a radical of the type alkyl or alkyl substituted by dialkylamino, phenyl, cycloalkyl (optionally substituted by —COOalk) or a saturated or unsaturated and mono- or bicyclic heterocycle having 3 to 10 ring members optionally comprising one or more heteroatoms chosen from oxygen, sulfur and nitrogen and optionally being substituted by one or more alkyl radicals,

R₁₀ and R₁₁, which are identical or different, represent a hydrogen atom or an alkyl radical or else R₁₀ and R₁₁ form, together with the nitrogen atom to which they are attached, a saturated mono- or bicyclic heterocycle having 3 to 10 ring members optionally comprising another heteroatom chosen from oxygen, sulfur and nitrogen and optionally being substituted by an alkyl radical,

R₁₂ and R₁₃, which are identical or different, represent a hydrogen atom or an alkyl or cycloalkyl radical or else R₁₂ and R₁₃ form, together with the nitrogen atom to which they are attached, a saturated mono- or bicyclic heterocycle having 3 to 10 ring members optionally comprising another heteroatom chosen from oxygen, sulfur and nitrogen and optionally being substituted by an alkyl, —COalk, —COOalk, —CO—NHalk, —CS—NHalk or —CO-alk-NR₁₄R₁₅ radical or a saturated mono- or

3

bicyclic heterocycle having 3 to 10 ring members and comprising a heteroatom chosen from oxygen, sulfur and nitrogen,

R₁₄ and R₁₅, which are identical or different, represent a hydrogen atom or an alkyl or —COOalk radical,

R₁₆ and R₁₇ form, together with the nitrogen atom to which they are attached, a saturated mono- or bicyclic heterocycle having 3 to 10 ring members optionally comprising another heteroatom chosen from oxygen, sulfur and nitrogen,

R' represents a hydrogen atom or a —CO-alk radical, or R represents a CHR₁₈ radical and

R₁₈ represents an —NHCOR₁₉ or —N(R₂₀)—Y—R₂₁ radical,

Y is CO or SO₂,

R₄ and R₃, which are identical or different, represent either an aromatic chosen from phenyl, naphthyl and indenyl, these aromatics being unsubstituted or substituted by one or more halogen, alkyl, alkoxy, formyl, hydroxyl, trifluoromethyl, trifluoromethoxy, —CO-alk, cyano, —COOH, —COOalk, —CONR₂₂R₂₃, —CO—NH—NR₂₄R₂₅, alkylsulfanyl, alkylsulfinyl, alkylsulfonyl, alkylsulfanylalkyl, alkylsulfinylalkyl, alkylsulfonylalkyl, hydroxyalkyl or -alk-NH₂R₂₃, or a heteroaromatic chosen from the benzofuryl, benzothiazolyl, benzothienyl, benzoxazolyl, chromanyl, 2,3-dihydrobenzofuryl, 2,3-dihydrobenzothienyl, pyrimidinyl, furyl, imidazolyl, isochromanyl, isoquinolyl, pyrrolyl, pyridyl, quinolyl, 1,2,3,4-tetrahydroisoquinolyl, thiazolyl and thienyl rings, it being possible for these heteroaromatics to be unsubstituted or substituted by a halogen, alkyl, alkoxy, hydroxyl, trifluoromethyl, trifluoromethoxy, cyano, —COOH, —COOalk, —CO—NH—NR₂₄R₂₅, —CONR₂₂R₂₃, -alk-NR₂₄R₂₅, alkylsulfanyl, alkylsulfinyl, alkylsulfonyl, alkylsulfanylalkyl, alkylsulfinylalkyl, alkylsulfonylalkyl or hydroxyalkyl,

R₁₉ represents an -alk-SO₂—R₂₆ radical, an -alk-SO₂—CH=CH—R₂₆ radical, a Het₁ radical substituted by —SO₂—R₂₆ or a phenyl radical substituted by —SO₂—R₂₆ or -alk-SO₂—R₂₆,

R₂₀ represents a hydrogen atom or an alkyl radical,

R₂₁ represents a phenylalkyl, Het₁ or Ar₁ radical,

R₂₂ and R₂₃, which are identical or different, represent a hydrogen atom or an alkyl radical or else R₂₂ and R₂₃ form, together with the nitrogen atom to which they are attached, a saturated mono- or bicyclic heterocycle having 3 to 10 ring members optionally comprising another heteroatom chosen from oxygen, sulfur and nitrogen and optionally being substituted by one or more alkyl,

R₂₄ and R₂₅, which are identical or different, represent a hydrogen atom or an alkyl, —COOalk, cycloalkyl, alkylcycloalkyl, -alk-O-alk or hydroxyalkyl radical or else R₂₄ and R₂₅ form, together with the nitrogen atom to which they are attached, a saturated or unsaturated mono- or bicyclic heterocycle having 3 to 10 ring members optionally comprising another heteroatom chosen from oxygen, sulfur and nitrogen and optionally being substituted by one or more alkyl, —COalk, —COOalk, —CO—NHalk, —CS—NHalk, oxo, hydroxyalkyl, -alk-O-alk or —CO—NH₂,

R₂₆ represents an alkyl, Ar₁ or Het₁ radical,

Ar₁ represents a phenyl, naphthyl or indenyl radical, these radicals optionally being substituted by one or more halogen, alkyl, alkoxy, cyano, —CO-alk, —COOH, —COOalk, —CONR₂₇R₂₈, —CO—NH—NR₂₉R₃₀, alkylsulfanyl, alkylsulfinyl, alkylsulfonyl, -alk-NR₂₉R₃₀, —NR₂₉R₃₀, alkylthioalkyl, formyl, hydroxyl, hydroxy-

4

alkyl, Het, —O-alk-NH-cycloalkyl, OCF₃, CF₃, —NH—CO-alk, —SO₂NH₂, —NH—COCH₃, —NH—COOalk or Het or else on 2 adjacent carbon atoms by dioxymethylene,

Het₁ represents an unsaturated or saturated mono- or bicyclic heterocycle having 3 to 10 ring members and comprising one or more heteroatoms chosen from oxygen, sulfur and nitrogen which is optionally substituted by one or more alkyl, alkoxy, vinyl, halogen, alkoxy carbonyl, oxo, hydroxyl, OCF₃ or CF₃, the nitrogenous heterocycles optionally being in their N-oxidized form,

R₂₇ and R₂₈, which are identical or different, represent a hydrogen atom or an alkyl radical or else R₂₇ and R₂₈ form, together with the nitrogen atom to which they are attached, a saturated mono- or bicyclic heterocycle having 3 to 10 ring members optionally comprising another heteroatom chosen from oxygen, sulfur and nitrogen and optionally being substituted by one or more alkyl radicals,

R₂₉ and R₃₀, which are identical or different, represent a hydrogen atom or an alkyl, —COOalk, cycloalkyl, alkylcycloalkyl, -alk-O-alk or hydroxyalkyl radical or else R₂₉ and R₃₀ form, together with the nitrogen atom to which they are attached, a saturated or unsaturated mono- or bicyclic heterocycle having 3 to 10 ring members optionally comprising another heteroatom chosen from oxygen, sulfur and nitrogen and optionally being substituted by one or more alkyl, —COalk, —COOalk, —CO—NHalk, —CS—NHalk, oxo, hydroxyalkyl, -alk-O-alk or —CO—NH₂ radicals,

or R represents CHR₃₁ and

R₃₁ represents an —N(R₃₂)R₃₃, —N(R₃₂)—CO—R₃₃ or —N(R₃₂)—SO₂R₃₄ radical,

R₄ and R₃, which are identical or different, represent either an aromatic chosen from phenyl, naphthyl and indenyl, these aromatics being unsubstituted or substituted by one or more halogen, alkyl, alkoxy, formyl, hydroxyl, trifluoromethyl, trifluoromethoxy, —CO-alk, cyano, —COOH, COOalk, —CONR₂₂R₂₃, —CO—NH—NR₂₄R₂₅, alkylsulfanyl, alkylsulfinyl, alkylsulfonyl, alkylsulfanylalkyl, alkylsulfinylalkyl, alkylsulfonylalkyl, hydroxyalkyl or -alk-NR₇R₈, or a heteroaromatic chosen from the benzofuryl, benzothiazolyl, benzothienyl, benzoxazolyl, chromanyl, 2,3-dihydrobenzofuryl, 2,3-dihydrobenzothienyl, furyl, imidazolyl, isochromanyl, isoquinolyl, pyrrolyl, pyridyl, pyrimidinyl, quinolyl, 1,2,3,4-tetrahydroisoquinolyl, thiazolyl and thienyl rings, it being possible for these heteroaromatics to be unsubstituted or substituted by a halogen, alkyl, alkoxy, hydroxyl, trifluoromethyl, trifluoromethoxy, cyano, —COOH, —COOalk, —CO—NH—NR₂₄R₂₅, —CONR₂₂R₂₃, -alk-NR₂₄R₂₅, alkylsulfanyl, alkylsulfinyl, alkylsulfonyl, alkylsulfanylalkyl, alkylsulfinylalkyl, alkylsulfonylalkyl or hydroxyalkyl,

R₃₂ represents a —C(R₃₅)(R₃₆)-Het₂, -Het₂, —C(R₃₅)(R₃₆)—Ar₂, Ar₂, cycloalkyl or norbornyl radical,

R₃₃ represents a hydrogen atom or a hydroxyalkyl, -alk-COOalk, -alk-CONR₂₂R₂₃, -alk-NR₂₂R₂₃, alkoxy, Ar₂, Het₂, —CH₂Ar₂, —CH₂Het₂ or alkyl radical, the latter optionally substituted by one or more halogen,

R₃₄ represents a hydroxyalkyl, -alk-COOalk, -alk-CONR₂₂R₂₃, -alk-NR₂₂R₂₃, alkoxy, Ar₂, Het₂, —CH₂Ar₂, —CH₂Het₂ or alkyl radical, the latter optionally substituted by one or more halogen,

R₃₅ represents a hydrogen atom or a hydroxyalkyl, -alk-COOalk, -alk-CONR₂₂R₂₃, -alk-NR₂₂R₂₃, alkoxyalkyl, Ar₂, Het₂, —CH₂Ar₂, —CH₂Het₂ or alkyl radical, the latter optionally substituted by one or more halogen,

5

R₃₆ represents a hydrogen atom or a hydroxyalkyl, -alk-COOalk, -alk-CONR₂₂R₂₃, -alk-NR₂₂R₂₃, alkoxyalkyl or alkyl radical, the latter optionally substituted by one or more halogen,

or else R₃₅ and R₃₆ form, together with the carbon atom to which they are attached, a saturated mono- or bicyclic ring having 3 to 10 ring members optionally comprising another heteroatom chosen from oxygen, sulfur and nitrogen and optionally being substituted by one or more alkyl,

Ar₂ represents a phenyl, naphthyl or indenyl radical, these various radicals optionally being substituted by one or more halogen, alkyl, alkoxy, —CO-alk, cyano, —COOH, —COOalk, —CONR₃₇R₃₈, —CO—NH—R₃₉R₄₀, alkyl-sulfanyl, alkylsulfanyl, alkylsulfonyl, -alk-NR₃₉R₄₀, —NR₃₉R₄₀, alkylthioalkyl, formyl, CF₃, OCF₃, Het, —O-alk-NH-cycloalkyl, SO₂NH₂, hydroxyl, hydroxyalkyl, —NHCOalk or NHCOOalk or on 2 adjacent carbon atoms by dioxymethylene,

Het₂ represents an unsaturated or saturated mono- or bicyclic heterocycle having 3 to 10 ring members and comprising one or more heteroatoms chosen from oxygen, sulfur and nitrogen which is optionally substituted by one or more alkyl, alkoxy, halogen, alkoxy-carbonyl, oxo or hydroxyl, the nitrogenous heterocycles optionally being in their N-oxidized form,

R₃₇ and R₃₈, which are identical or different, represent a hydrogen atom or an alkyl radical or else R₃₇ and R₃₈ form, together with the nitrogen atom to which they are attached, a saturated mono- or bicyclic heterocycle having 3 to 10 ring members optionally comprising another heteroatom chosen from oxygen, sulfur and nitrogen and optionally being substituted by one or more alkyl,

R₃₉ and R₄₀, which are identical or different, represent a hydrogen atom or an alkyl radical or else R₃₉ and R₄₀ form, together with the nitrogen atom to which they are attached, a saturated mono- or bicyclic heterocycle having 3 to 10 ring members optionally comprising another heteroatom chosen from oxygen, sulfur and nitrogen and optionally being substituted by one or more alkyl,

alk represents an alkyl or alkylene radical,

the alkyl and alkylene radicals and portions and the alkoxy radicals and portions have straight or branched chains and comprise 1 to 6 carbon atoms and the cycloalkyl radicals comprise 3 to 10 carbon atoms,

the optical isomers of these compounds and their pharmaceutically acceptable salts with an inorganic or organic acid.

The preferred azetidine derivatives are as follows:

1-benzhydryl-3-[(methylsulfonyl)(phenyl)methylene]azetidine,

1-benzhydryl-3-[(3-methylphenyl)(methylsulfonyl)methylene]azetidine,

1-benzhydryl-3-[(3-chlorophenyl)(methylsulfonyl)methylene]azetidine,

1-benzhydryl-3-[(3,5-dichlorophenyl)(methylsulfonyl)methylene]azetidine,

1-benzhydryl-3-[(2,5-dichlorophenyl)(methylsulfonyl)methylene]azetidine,

1-benzhydryl-3-[(2,3-dichlorophenyl)(methylsulfonyl)methylene]azetidine,

1-benzhydryl-3-[(3-fluorophenyl)(methylsulfonyl)methylene]azetidine,

1-benzhydryl-3-[(3,5-difluorophenyl)(methylsulfonyl)methylene]azetidine,

1-benzhydryl-3-[(3-bromophenyl)(methylsulfonyl)methylene]azetidine,

6

1-benzhydryl-3-[(3-iodophenyl)(methylsulfonyl)methylene]azetidine,

1-benzhydryl-3-[(methylsulfonyl)(3-trifluoromethoxyphenyl)methylene]azetidine,

5 1-benzhydryl-3-[(methylsulfonyl)(3-trifluoromethylphenyl)methylene]azetidine,

1-benzhydryl-3-[[3,5-bis(trifluoromethyl)phenyl](methylsulfonyl)methylene]azetidine,

1-benzhydryl-3-[(3,5-dibromophenyl)(methylsulfonyl)methylene]azetidine,

10 1-benzhydryl-3-[(3-methoxycarbonylphenyl)(methylsulfonyl)methylene]azetidine,

1-benzhydryl-3-[(3-cyanophenyl)(methylsulfonyl)methylene]azetidine,

15 1-benzhydryl-3-[(3-carbamoylphenyl)(methylsulfonyl)methylene]azetidine,

1-benzhydryl-3-[(methylsulfonyl)(naphth-1-yl)(methylsulfonyl)methylene]azetidine,

1-[bis(4-chlorophenyl)methyl]-3-[(3,5-difluorophenyl)(methylsulfonyl)methylene]azetidine,

20 1-[bis(4-methoxyphenyl)methyl]-3-[(3,5-difluorophenyl)(methylsulfonyl)methylene]azetidine,

1-[bis(4-methylphenyl)methyl]-3-[(3,5-difluorophenyl)(methylsulfonyl)methylene]azetidine,

25 (RS)-3-[(3,5-difluorophenyl)(methylsulfonyl)methylene]-1-[4-methoxyphenyl(phenyl)methyl]azetidine,

(R)-3-[(3,5-difluorophenyl)(methylsulfonyl)methylene]-1-[4-methoxyphenyl(phenyl)methyl]azetidine,

30 (S)-3-[(3,5-difluorophenyl)(methylsulfonyl)methylene]-1-[4-methoxyphenyl(phenyl)methyl]azetidine,

1-[bis(4-trifluoromethoxyphenyl)methyl]-3-[(3,5-difluorophenyl)(methylsulfonyl)methylene]azetidine,

1-[bis(4-trifluoromethylphenyl)methyl]-3-[(3,5-difluorophenyl)(methylsulfonyl)methylene]azetidine,

35 1-[bis(4-chlorophenyl)methyl]-3-[[3,5-bis(trifluoromethyl)phenyl]methylsulfonylmethylene]azetidine,

(RS)-1-[4-chlorophenyl(2,4-dichlorophenyl)methyl]-3-[(3,5-difluorophenyl)(methylsulfonyl)methylene]azetidine,

40 (R)-1-[4-chlorophenyl(2,4-dichlorophenyl)methyl]-3-[(3,5-difluorophenyl)(methylsulfonyl)methylene]azetidine,

(S)-1-[4-chlorophenyl(2,4-dichlorophenyl)methyl]-3-[(3,5-difluorophenyl)(methylsulfonyl)methylene]azetidine,

45 (RS)-1-[(4-chlorophenyl)[4-(hydroxymethyl)phenyl]methyl]-3-[(3,5-difluorophenyl)(methylsulfonyl)methylene]azetidine,

(R)-1-[(4-chlorophenyl)[4-(hydroxymethyl)phenyl]methyl]-3-[(3,5-difluorophenyl)(methylsulfonyl)methylene]azetidine,

50 (S)-1-[(4-chlorophenyl)[4-(hydroxymethyl)phenyl]methyl]-3-[(3,5-difluorophenyl)(methylsulfonyl)methylene]azetidine,

(RS)-1-[(4-chlorophenyl)[4-(pyrrolidylmethyl)phenyl]methyl]-3-[(3,5-difluorophenyl)(methylsulfonyl)methylene]azetidine,

55 (R)-1-[(4-chlorophenyl)[4-(pyrrolidylmethyl)phenyl]methyl]-3-[(3,5-difluorophenyl)(methylsulfonyl)methylene]azetidine,

(S)-1-[(4-chlorophenyl)[4-(pyrrolidylmethyl)phenyl]methyl]-3-[(3,5-difluorophenyl)(methylsulfonyl)methylene]azetidine,

60 1-[(RS)-(4-chlorophenyl)[4-(3,3-dimethylpiperidin-1-ylmethyl)phenyl]methyl]-3-[(3,5-difluorophenyl)(methylsulfonyl)methylene]azetidine,

65 1-[(R)-(4-chlorophenyl)[4-(3,3-dimethylpiperidin-1-ylmethyl)phenyl]methyl]-3-[(3,5-difluorophenyl)(methylsulfonyl)methylene]azetidine,

(R)-1-[(4-chlorophenyl)[4-(N-ethylcarbamoyl)phenyl]methyl]-3-[(3,5-difluorophenyl)(methylsulfonyl)methylene]azetidine,
 (S)-1-[(4-chlorophenyl)[4-(N-ethylcarbamoyl)phenyl]methyl]-3-[(3,5-difluorophenyl)(methylsulfonyl)methylene]azetidine,
 (RS)-1-[(4-carbamoylphenyl)(4-chlorophenyl)methyl]-3-[(3,5-difluorophenyl)(methylsulfonyl)methylene]azetidine,
 (R)-1-[(4-carbamoylphenyl)(4-chlorophenyl)methyl]-3-[(3,5-difluorophenyl)(methylsulfonyl)methylene]azetidine,
 (S)-1-[(4-carbamoylphenyl)(4-chlorophenyl)methyl]-3-[(3,5-difluorophenyl)(methylsulfonyl)methylene]azetidine,
 1-[bis(4-chlorophenyl)methyl]-3-[(3,5-dichlorophenyl)(methylsulfonyl)methylene]azetidine,
 1-benzhydryl-3-[(3-methylsulfonylphenyl)(methylsulfonyl)methylene]azetidine,
 1-benzhydryl-3-[(3-methylsulfonylmethyl)phenyl](methylsulfonyl)methylene]azetidine,
 1-[bis(4-chlorophenyl)methyl]-3-[(3-cyanophenyl)(methylsulfonyl)methylene]azetidine,
 1-[bis(4-chlorophenyl)methyl]-3-[(3-carbamoylphenyl)(methylsulfonyl)methylene]azetidine,
 1-[bis(4-chlorophenyl)methyl]-3-[(3-methoxyphenyl)(methylsulfonyl)methylene]azetidine,
 1-[bis(4-chlorophenyl)methyl]-3-[(3-hydroxyphenyl)(methylsulfonyl)methylene]azetidine,
 1-[bis(4-chlorophenyl)methyl]-3-[(methylsulfonyl)(3-pyrrolidinylphenyl)methylene]azetidine,
 1-[bis(4-chlorophenyl)methyl]-3-[(3-hydroxymethylphenyl)(methylsulfonyl)methylene]azetidine,
 1-[bis(4-chlorophenyl)methyl]-3-[(methylsulfonyl)[3-(N-piperidylcarbamoyl)phenyl]methylene]azetidine,
 1-[bis(4-chlorophenyl)methyl]-3-[(methylsulfonyl)(3-trifluoromethylsulfonylphenyl)(methylsulfonyl)methylene]azetidine,
 1-[bis(4-fluorophenyl)methyl]-3-[(3,5-difluorophenyl)(methylsulfonyl)methylene]azetidine,
 1-[bis(2-fluorophenyl)methyl]-3-[(3,5-difluorophenyl)(methylsulfonyl)methylene]azetidine,
 1-[bis(3-fluorophenyl)methyl]-3-[(3,5-difluorophenyl)(methylsulfonyl)methylene]azetidine,
 (RS)-1-[(4-chlorophenyl)(thiazol-2-yl)methyl]-3-[(methylsulfonyl)(phenyl)methylene]azetidine,
 (R)-1-[(4-chlorophenyl)(thiazol-2-yl)methyl]-3-[(methylsulfonyl)(phenyl)methylene]azetidine,
 (S)-1-[(4-chlorophenyl)(thiazol-2-yl)methyl]-3-[(methylsulfonyl)(phenyl)methylene]azetidine,
 (RS)-1-[(4-chlorophenyl)(thien-2-yl)methyl]-3-[(3,5-difluorophenyl)(methylsulfonyl)methylene]azetidine,
 (R)-1-[(4-chlorophenyl)(thien-2-yl)methyl]-3-[(3,5-difluorophenyl)(methylsulfonyl)methylene]azetidine,
 (S)-1-[(4-chlorophenyl)(thien-2-yl)methyl]-3-[(3,5-difluorophenyl)(methylsulfonyl)methylene]azetidine,
 1-benzhydryl-3-[(ethylsulfonyl)(phenyl)methylene]azetidine,
 1-[bis(4-chlorophenyl)methyl]-3-[(3-[N-(4-methylpiperazinyl)carbamoyl]phenyl)(methylsulfonyl)methylene]azetidine,
 1-[bis(4-chlorophenyl)methyl]-3-[(3-(2,2-dimethylcarbohydrazido)phenyl)(methylsulfonyl)methylene]azetidine,
 1-[bis(thien-2-yl)methyl]-3-[(3,5-difluorophenyl)(methylsulfonyl)methylene]azetidine,
 1-[bis(p-tolyl)methyl]-3-[(methylsulfonyl)(phenyl)methylene]azetidine,
 1-[(4-chlorophenyl)(4-hydroxymethylphenyl)methyl]-3-[(3,5-difluorophenyl)(methylsulfonyl)methylene]azetidine,

1-[bis(4-chlorophenyl)methyl]-3-[(3-methylaminophenyl)(methylsulfonyl)methylene]azetidine,
 (RS)-1-[(4-chlorophenyl)(thiazol-2-yl)methyl]-3-[(3,5-difluorophenyl)(methylsulfonyl)methylene]azetidine,
 (R)-1-[(4-chlorophenyl)(thiazol-2-yl)methyl]-3-[(3,5-difluorophenyl)(methylsulfonyl)methylene]azetidine,
 (S)-1-[(4-chlorophenyl)(thiazol-2-yl)methyl]-3-[(3,5-difluorophenyl)(methylsulfonyl)methylene]azetidine,
 1-[bis(4-chlorophenyl)methyl]-3-[(methylsulfonyl)(2-methoxycarbonylthien-5-yl)methylene]azetidine,
 (RS)-1-[bis(4-chlorophenyl)methyl]-3-hydroxy-3-[(methylsulfonyl)(2-methoxycarbonylthien-5-yl)methyl]azetidine,
 1-[bis(4-chlorophenyl)methyl]-3-[(2-isobutylaminocarbonylthien-5-yl)(methylsulfonyl)methylene]azetidine,
 1-[bis(4-chlorophenyl)methyl]-3-[(RS)-(3-methoxycarbonylphenyl)(methylsulfonyl)methyl]azetidin-3-ol,
 1-[bis(4-chlorophenyl)methyl]-3-[(RS)-(methylsulfonyl)(pyridin-4-yl)methyl]azetidin-3-ol,
 1-[bis(4-chlorophenyl)methyl]-3-[(RS)-(methylsulfonyl)(pyridin-3-yl)methyl]azetidin-3-ol,
 3-({1-[bis(4-chlorophenyl)methyl]azetidin-3-ylidene}(methanesulfonyl)methyl)-N-(3-(morpholin-4-yl)propyl)benzamide,
 3-({1-[bis(4-chlorophenyl)methyl]azetidin-3-ylidene}(methanesulfonyl)methyl)-N-(3-dimethylaminopropyl)benzamide,
 3-({1-[bis(4-chlorophenyl)methyl]azetidin-3-ylidene}(methanesulfonyl)methyl)-N-(2-(pyrrolidin-1-yl)ethyl)benzamide,
 3-({1-[bis(4-chlorophenyl)methyl]azetidin-3-ylidene}(methanesulfonyl)methyl)-N-(2-dimethylamino-1-methylethyl)benzamide,
 3-({1-[bis(4-chlorophenyl)methyl]azetidin-3-ylidene}(methanesulfonyl)methyl)-N-(piperidin-1-yl)benzamide,
 3-({1-[bis(4-chlorophenyl)methyl]azetidin-3-ylidene}(methanesulfonyl)methyl)-N-isobutylbenzamide,
 3-({1-[bis(4-chlorophenyl)methyl]azetidin-3-ylidene}(methanesulfonyl)methyl)-N-(3-(imidazol-1-yl)propyl)benzamide,
 3-({1-[bis(4-chlorophenyl)methyl]azetidin-3-ylidene}(methanesulfonyl)methyl)-N-(2-dimethylaminoethyl)benzamide,
 N¹-methylhydrazide of 3-({1-[bis(4-chlorophenyl)methyl]azetidin-3-ylidene}(methanesulfonyl)methyl)benzoic acid,
 3-({1-[bis(4-chlorophenyl)methyl]azetidin-3-ylidene}(methanesulfonyl)methyl)-N-(2-(morpholin-4-yl)ethyl)benzamide,
 3-({1-[bis(4-chlorophenyl)methyl]azetidin-3-ylidene}(methanesulfonyl)methyl)-N-(1-ethylpyrrolidin-2-ylmethyl)benzamide,
 3-({1-[bis(4-chlorophenyl)methyl]azetidin-3-ylidene}(methanesulfonyl)methyl)-N-(2,2-dimethylpropyl)benzamide,
 3-({1-[bis(4-chlorophenyl)methyl]azetidin-3-ylidene}(methanesulfonyl)methyl)-N-(cyclohexylmethyl)benzamide,
 3-({1-[bis(4-chlorophenyl)methyl]azetidin-3-ylidene}(methanesulfonyl)methyl)-N-(cyclopropylmethyl)benzamide,
 3-({1-[bis(4-chlorophenyl)methyl]azetidin-3-ylidene}(methanesulfonyl)methyl)-N-(2-methylbutyl)benzamide,
 3-({1-[bis(4-chlorophenyl)methyl]azetidin-3-ylidene}(methanesulfonyl)methyl)-N-(2-phenylpropyl)benzamide,

11

3-({1-[bis(4-chlorophenyl)methyl]azetid-3-ylidene} (methanesulfonyl)methyl)-N-(tetrahydrofuran-2-ylmethyl)benzamide,
 3-({1-[bis(4-chlorophenyl)methyl]azetid-3-ylidene} (methanesulfonyl)methyl)-N-(2,2-diphenylethyl)benzamide,
 3-({1-[bis(4-chlorophenyl)methyl]azetid-3-ylidene} (methanesulfonyl)methyl)-N-(2-ethylbutyl)benzamide, methyl ester of 4-{{3-({1-[bis(4-chlorophenyl)methyl]azetid-3-ylidene} (methanesulfonyl)methyl)benzoylamino} methyl}cyclohexanecarboxylic acid,
 2-amino-1-{{4-{{3-({1-[bis(4-chlorophenyl)methyl]azetid-3-ylidene} (methanesulfonyl)methyl)phenyl}piperazin-1-yl}ethanone},
 tert-butyl ester of (2-{{4-{{3-({1-[bis(4-chlorophenyl)methyl]azetid-3-ylidene} (methanesulfonyl)methyl)phenyl}piperazin-1-yl}-2-oxoethyl)carbamic acid,
 1-{{4-{{3-({1-[bis(4-chlorophenyl)methyl]azetid-3-ylidene} (methanesulfonyl)methyl)phenyl}piperazin-1-yl}-2-(methylamino)ethanone},
 tert-butyl ester of (2-{{4-{{3-({1-[bis(4-chlorophenyl)methyl]azetid-3-ylidene} (methanesulfonyl)methyl)phenyl}piperazin-1-yl}-2-oxoethyl)-N-methylcarbamic acid,
 N-methylamide of 4-{{3-({1-[bis(4-chlorophenyl)methyl]azetid-3-ylidene} (methanesulfonyl)methyl)phenyl}piperazine-1-carbothioic acid},
 N-methylamide of 4-{{3-({1-[bis(4-chlorophenyl)methyl]azetid-3-ylidene} (methanesulfonyl)methyl)phenyl}piperazine-1-carboxylic acid},
 methyl ester of 4-{{3-({1-[bis(4-chlorophenyl)methyl]azetid-3-ylidene} (methanesulfonyl)methyl)-phenyl}piperazine-1-carboxylic acid},
 1-{{3-({1-[bis(4-chlorophenyl)methyl]azetid-3-ylidene} (methanesulfonyl)methyl)phenyl}-4-isobutylpiperazine},
 1-{{3-({1-[bis(4-chlorophenyl)methyl]azetid-3-ylidene} (methanesulfonyl)methyl)phenyl}-4-ethylpiperazine},
 4-acetyl-1-{{3-({1-[bis(4-chlorophenyl)methyl]azetid-3-ylidene} (methanesulfonyl)methyl)phenyl}piperazine},
 1-{{4-{{3-({1-[bis(4-chlorophenyl)methyl]azetid-3-ylidene} (methanesulfonyl)methyl)phenyl}piperazin-1-yl}-2-dimethylaminoethanone},
 1-{{3-({1-[bis(4-chlorophenyl)methyl]azetid-3-ylidene} (methanesulfonyl)methyl)phenyl}piperazine},
 tert-butyl ester of 4-{{3-({1-[bis(4-chlorophenyl)methyl]azetid-3-ylidene} (methanesulfonyl)methyl)-phenyl}piperazine-1-carboxylic acid},
 1-{{bis(4-methoxycarbonylphenyl)methyl}-3-{{3,5-difluorophenyl}(methylsulfonyl)methylene}azetidine},
 3-acetoxy-1-{{bis(4-methoxycarbonylphenyl)methyl}-3-{{(RS)-(3,5-difluorophenyl)(methylsulfonyl)methyl}azetidine},
 (RS)-4-{{4-{{(4-chlorophenyl)}3-{{3,5-difluorophenyl}(methanesulfonyl)methylene}azetid-1-yl}methyl}benzyl}morpholine},
 4-{{4-{{3-{{(1-benzhydrylazetid-3-ylidene)(methanesulfonyl)methyl}phenoxy}butyl}morpholine},
 4-{{4-{{3-{{(1-benzhydrylazetid-3-ylidene)(methanesulfonyl)methyl}phenoxy}propyl}morpholine},
 N-{{1-[bis(4-chlorophenyl)methyl]azetid-3-yl}thien-2-yl} sulfonamide},
 N-{{1-[bis(4-chlorophenyl)methyl]azetid-3-yl}-4-methoxyphenyl} sulfonamide},
 N-{{4-(N-{{1-[bis(4-chlorophenyl)methyl]azetid-3-yl} sulfamoyl)phenyl}acetamide},
 N-{{1-[bis(4-chlorophenyl)methyl]azetid-3-yl}-4-methylphenyl} sulfonamide},

12

N-{{1-[bis(4-chlorophenyl)methyl]azetid-3-yl}-3,4-dimethoxyphenyl} sulfonamide,
 N-{{1-[bis(4-chlorophenyl)methyl]azetid-3-yl}-3-fluorophenyl} sulfonamide,
 5 N-{{1-[bis(4-chlorophenyl)methyl]azetid-3-yl}-3,4-dichlorophenyl} sulfonamide},
 N-{{1-[bis(4-chlorophenyl)methyl]azetid-3-yl}-3-cyanophenyl} sulfonamide},
 N-{{1-[bis(4-chlorophenyl)methyl]azetid-3-yl}-2,5-dimethoxyphenyl} sulfonamide},
 10 N-{{1-[bis(4-chlorophenyl)methyl]azetid-3-yl}-3-trifluoromethylphenyl} sulfonamide},
 N-{{1-[bis(4-chlorophenyl)methyl]azetid-3-yl}naphth-2-yl} sulfonamide},
 15 N-{{1-[bis(4-chlorophenyl)methyl]azetid-3-yl}naphth-1-yl} sulfonamide},
 N-{{1-[bis(4-chlorophenyl)methyl]azetid-3-yl}-3,4-difluorophenyl} sulfonamide},
 N-{{1-[bis(4-chlorophenyl)methyl]azetid-3-yl}-1-methyl-1H-imidazol-4-yl} sulfonamide},
 20 N-{{4-(N-{{1-[bis(4-chlorophenyl)methyl]azetid-3-yl} sulfamoyl)-2-chlorophenyl}acetamide},
 N-{{1-[bis(4-chlorophenyl)methyl]azetid-3-yl}pyrid-3-yl} sulfonamide},
 25 N-{{1-[bis(4-chlorophenyl)methyl]azetid-3-yl}-4-fluorophenyl} sulfonamide},
 N-{{1-[bis(4-chlorophenyl)methyl]azetid-3-yl}quinol-8-yl} sulfonamide},
 N-{{1-[bis(4-chlorophenyl)methyl]azetid-3-yl}phenyl} sulfonamide},
 30 N-{{1-[bis(4-chlorophenyl)methyl]azetid-3-yl}(phenylmethyl) sulfonamide},
 N-{{1-[bis(4-chlorophenyl)methyl]azetid-3-yl}-3,5-difluorophenyl} sulfonamide},
 35 N-{{1-[bis(4-chlorophenyl)methyl]azetid-3-yl}pyrid-2-yl} sulfonamide},
 N-{{1-[bis(4-chlorophenyl)methyl]azetid-3-yl}(3-fluoro-5-pyrrolidin-1-ylphenyl) sulfonamide},
 N-{{1-[bis(4-chlorophenyl)methyl]azetid-3-yl}-N-methyl-4-fluorophenyl} sulfonamide},
 40 N-{{1-[bis(4-chlorophenyl)methyl]azetid-3-yl}-N-methylquinol-8-yl} sulfonamide},
 N-{{1-[bis(4-chlorophenyl)methyl]azetid-3-yl}-N-methylphenyl} sulfonamide},
 45 N-{{1-[bis(4-chlorophenyl)methyl]azetid-3-yl}-N-methyl(phenylmethyl) sulfonamide},
 N-{{1-[bis(4-chlorophenyl)methyl]azetid-3-yl}-3-sulfamoylphenyl} sulfonamide},
 50 2-benzenesulfonyl-N-{{1-[bis(4-chlorophenyl)methyl]azetid-3-yl}acetamide},
 N-{{1-[bis(4-chlorophenyl)methyl]azetid-3-yl}-2-(4-toluene-4-sulfonyl)acetamide},
 (3-chloro-4-{{(methylsulfonyl)thiophene-2-carboxy}}1-{{bis(4-chlorophenyl)methyl}azetid-3-yl}amide},
 55 N-{{1-[bis(4-chlorophenyl)methyl]azetid-3-yl}-3-(2-phenylethylsulfonyl)propionamide},
 N-{{1-[bis(4-chlorophenyl)methyl]azetid-3-yl}-4-(methylsulfonyl)benzamide},
 60 N-{{1-[bis(4-chlorophenyl)methyl]azetid-3-yl}-4-(methanesulfonyl)benzamide},
 (5-{{(methylsulfonyl)thiophene-2-carboxy}}1-{{bis(4-chlorophenyl)methyl}azetid-3-yl}amide},
 (5-methylsulfonyl-3-methyl-4-vinylthiophene-2-carboxy){{1-[bis(4-chlorophenyl)methyl]azetid-3-yl}amide},
 65 (RS)-N-{{1-{{(4-chlorophenyl)(pyridin-3-yl)methyl}azetid-3-yl}-3,5-difluorobenzenesulfonyl} sulfonamide},

(RS)-N-{1-[(4-chlorophenyl)(pyrimidin-5-yl)methyl]azetid-
din-3-yl}-3,5-difluorobenzenesulfonamide,
N-{1-[bis(4-chlorophenyl)methyl]azetid-3-yl}-N-(6-chlo-
ropyrid-2-yl)methylsulfonamide,
N-{1-[bis(4-chlorophenyl)methyl]azetid-3-yl}-N-(6-eth-
ylpyrid-2-yl)methylsulfonamide,
N-{1-[bis(4-chlorophenyl)methyl]azetid-3-yl}-N-(quinol-
6-yl)methylsulfonamide,
N-{1-[bis(4-chlorophenyl)methyl]azetid-3-yl}-N-(quinol-
5-yl)methylsulfonamide,
N-{1-[bis(4-chlorophenyl)methyl]azetid-3-yl}-N-(iso-
quinol-5-yl)methylsulfonamide,
N-{1-[bis(4-chlorophenyl)methyl]azetid-3-yl}-N-(pyrid-
3-yl)methylsulfonamide,
N-{1-[bis(4-chlorophenyl)methyl]azetid-3-yl}-N-(pyrid-
1-oxide-3-yl)methylsulfonamide,
N-(1R,2S,4S)-(bicyclo[2.2.1]hept-2-yl)-N-{1-[bis-(4-chlo-
rophenyl)methyl]azetid-3-yl}methylsulfonamide,
N-(1R,2R,4S)-(bicyclo[2.2.1]hept-2-yl)-N-{1-[bis-(4-chlo-
rophenyl)methyl]azetid-3-yl}methylsulfonamide,
N-{1-[bis(4-chlorophenyl)methyl]azetid-3-yl}-N-(3,5-di-
fluorophenyl)methylsulfonamide,
N-{1-[bis(4-chlorophenyl)methyl]azetid-3-yl}-N-(thia-
zol-2-yl)methylsulfonamide,
N-{1-[bis(4-chlorophenyl)methyl]azetid-3-yl}-N-(3-
methoxyphenyl)methylsulfonamide,
N-{1-[bis(4-chlorophenyl)methyl]azetid-3-yl}-N-(3-hy-
droxyphenyl)methylsulfonamide,
N-{1-[bis(4-chlorophenyl)methyl]azetid-3-yl}-N-(3-(hy-
droxymethyl)phenyl)methylsulfonamide,
ethyl N-{1-[bis(4-chlorophenyl)methyl]azetid-3-yl}-N-
(methylsulfonyl)-3-aminobenzoate,
N-{1-[bis(4-chlorophenyl)methyl]azetid-3-yl}-N-(isobu-
tylpiperid-4-yl)methylsulfonamide,
N-benzyl-N-{1-[bis(4-chlorophenyl)methyl]azetid-3-
yl}amine,
N-{1-[bis(4-chlorophenyl)methyl]azetid-3-yl}-N-(3,5-di-
fluorobenzyl)amine,
N-{1-[bis(4-chlorophenyl)methyl]azetid-3-yl}-N-(3,5-di-
fluorobenzyl)methylsulfonamide,
N-{1-[bis(4-chlorophenyl)methyl]azetid-3-yl}-N-(pyrid-
3-ylmethyl)methylsulfonamide,
N-{1-[bis(4-fluorophenyl)methyl]azetid-3-yl}-N-(3,5-dif-
luorophenyl)methylsulfonamide,
(RS)-N-{1-[(4-chlorophenyl)(pyrid-3-yl)methyl]azetid-3-
yl}-N-(3,5-difluorophenyl)methylsulfonamide,
(R)-N-{1-[(4-chlorophenyl)(pyrid-3-yl)methyl]azetid-3-
yl}-N-(3,5-difluorophenyl)methylsulfonamide,
(S)-N-{1-[(4-chlorophenyl)(pyrid-3-yl)methyl]azetid-3-
yl}-N-(3,5-difluorophenyl)methylsulfonamide,
(RS)-N-{1-[(4-chlorophenyl)(pyrid-4-yl)methyl]azetid-3-
yl}-N-(3,5-difluorophenyl)methylsulfonamide,
(R)-N-{1-[(4-chlorophenyl)(pyrid-4-yl)methyl]azetid-3-
yl}-N-(3,5-difluorophenyl)methylsulfonamide,
(S)-N-{1-[(4-chlorophenyl)(pyrid-4-yl)methyl]azetid-3-
yl}-N-(3,5-difluorophenyl)methylsulfonamide,
(RS)-N-{1-[(4-chlorophenyl)(pyrimidin-5-yl)methyl]azeti-
din-3-yl}-N-(3,5-difluorophenyl)methylsulfonamide,
(R)-N-{1-[(4-chlorophenyl)(pyrimidin-5-yl)methyl]azeti-
din-3-yl}-N-(3,5-difluorophenyl)methylsulfonamide,
(S)-N-{1-[(4-chlorophenyl)(pyrimidin-5-yl)methyl]azeti-
din-3-yl}-N-(3,5-difluorophenyl)methylsulfonamide,
N-{1-[bis(4-chlorophenyl)methyl]azetid-3-yl}-N-(3,5-di-
fluorophenyl)benzylsulfonamide,

their optical isomers and their pharmaceutically acceptable salts with an inorganic or organic acid.

And even more particularly preferred are the following azetidine derivatives:

1-[bis(4-chlorophenyl)methyl]-3-[(RS)-(3,5-difluorophe-
nyl)(methylsulfonyl)methyl]azetid-3-ol,
3-acetoxy-1-[bis(4-chlorophenyl)methyl]-3-[(RS)-(3,5-dif-
luorophenyl)(methylsulfonyl)methyl)methylsulfonylm-
ethyl]azetidine,
1-[bis(4-chlorophenyl)methyl]-3-[(3,5-difluorophenyl)(me-
thylsulfonyl)methylene]azetidine,

10 their optical isomers and their pharmaceutically acceptable salts with an inorganic or organic acid.

Mention may be made, as examples of pharmaceutically acceptable salts of the azetidine derivatives, of the following salts: benzenesulfonate, hydrobromide, hydrochloride, cit-
rate, ethanesulfonate, fumarate, gluconate, iodate, isethion-
ate, maleate, methanesulfonate, methylenebis- β -oxynaph-
thoate, nitrate, oxalate, pamoate, phosphate, salicylate,
succinate, sulfate, tartrate, theophyllinacetate and p-toluene-
sulfonate.

Other CB1 receptor antagonists of use in the combina-
tions according to the invention are, for example, the pyra-
zole derivatives disclosed in EP 576 357, EP 658 546, EP
656 354, WO 97/19063 and WO 00/46209, the ben-
zothiofene and benzofuran derivatives disclosed in WO
96/02248 or the arylsulfonamides disclosed in WO
98/37061. Mention may in particular be made of the prod-
ucts known under the code SR141716 and LY320135.

The synergistic effect of the combination of sibutramine
and of a CB1 receptor antagonist on food intake was
determined according to the following protocol:

Obese Fa/fa Zucker rats aged 7 weeks and originating
from Iffa-Credo, France, were used in this study. The rats are
housed in individual cages and weighed every day between
8 and 10 o'clock in the morning. The amount of food is also
weighed each morning at the same time. This food (M20,
Pietrement, France) is changed every day and the rats have
free access thereto for 24 hours. All the rats are treated for
a week with the vehicle (miglyol 812N and 0.5% methyl-
cellulose/0.2% polysorbate 80) in two consecutive admin-
istrations. The rats are treated from the 8th day with the
vehicle, the CB1 receptor antagonist (1[bis(4-chlorophenyl)
methyl]-3-[(3,5-difluorophenyl)(methylsulfonyl)methyl-
ene]azetidine) or sibutramine by the oral route (see table
below).

The sibutramine is dissolved in a 0.5% methylcellulose/
0.2% polysorbate 80 solution and administered at a dose of
3 mg/kg; the CB1 receptor antagonist is dissolved in miglyol
812N (Hüls, Germany) at a dose of 0.6 mg/kg and the two
products are administered under a volume of 1 ml/kg. Each
group is composed of 12 to 14 animals. The following
groups are formed and the animals are treated for five days
at the rate of two consecutive administrations every day.

GROUP	First administration	Second administration
1	miglyol	0.5% methylcellulose/ 0.2% polysorbate
"vehicle group"		
2	miglyol	sibutramine 3 mg/kg
"sibutramine group"		
3	CB1 receptor antagonist	0.5% methylcellulose/ 0.2% polysorbate
"CB1 receptor antagonist group"		
4	CB1 receptor	sibutramine 3 mg/kg

-continued

GROUP	First administration	Second administration
"combination group"	antagonist 0.6 mg/kg	

The food consumption of each animal is measured every day. The results are expressed as mean amount of food consumed during the 5 days of treatment. The results obtained are given in the table below.

Treatment	Food consumption during the 5 days of treatment (g)
Vehicles	25.52 ± 0.30
sibutramine 3 mg/kg	24.60 ± 0.32*
CB1 receptor antagonist 0.6 mg/kg	24.00 ± 0.24**
sibutramine (3 mg/kg) + CB1 receptor antagonist (0.6 mg/kg)	22.76 ± 0.02***

*p < 0.05

**p < 0.01

***p < 0.0001

The results show that, in the animals receiving the sibutramine and CB1 receptor antagonist combination, the reduction in food consumption is much greater than that of the animals treated either with sibutramine alone or with the CB1 receptor antagonist alone.

The compounds of the combination can be employed orally, parenterally, transdermally or rectally, either simultaneously or separately or spread out over time.

The present invention also relates to the pharmaceutical compositions comprising the combination of sibutramine, its hydrate or one of its pharmaceutically acceptable salts and of a CB1 receptor antagonist in the pure state or with one or more compatible and pharmacologically acceptable diluents and/or adjuvants and/or optionally in combination with another pharmaceutically compatible and physiologically active product for a use which is either simultaneous or separate or spread out over time.

Use may be made, as solid compositions for oral administration, of tablets, pills, powders (hard gelatin capsules, cachets) or granules. In these compositions, the active principles are mixed with one or more inert diluents, such as starch, cellulose, sucrose, lactose or silica, under an argon stream. These compositions can also comprise substances other than the diluents, for example one or more lubricants such as magnesium stearate or talc, a colorant, a coating (dragées) or a glaze.

Use may be made, as liquid compositions for oral administration, of pharmaceutically acceptable solutions, suspensions, emulsions, syrups and elixirs comprising inert diluents, such as water, ethanol, glycerol, vegetable oils or liquid paraffin. These compositions can comprise substances other than the diluents, for example wetting, sweetening, thickening, flavouring or stabilizing products.

The sterile compositions for parenteral administration can preferably be solutions in aqueous or nonaqueous form, suspensions or emulsions. Use may be made, as solvent or vehicle, of water, propylene glycol, a polyethylene glycol, vegetable oils, in particular olive oil, injectable organic esters, for example ethyl oleate, or other suitable organic solvents. These compositions can also comprise adjuvants,

in particular wetting, isotonicizing, emulsifying, dispersing and stabilizing agents. Sterilization can be carried out in several ways, for example by aseptic filtration, by incorporating sterilizing agents in the composition, by irradiation or by heating. They can also be prepared in the form of sterile solid compositions which can be dissolved at the time of use in sterile water or any other injectable sterile medium.

The compositions for rectal administration are suppositories or rectal capsules which comprise, in addition to the active product, excipients such as cocoa butter, semisynthetic glycerides or polyethylene glycols.

The pharmaceutical compositions generally comprise 0.5 to 10 mg of sibutramine and 0.1 to 200 mg of the CB1 receptor antagonist.

The present invention also relates to the method for the treatment of obesity which consists in administering, to the patient, a combination according to the invention either simultaneously or separately or spread out over time.

The doses depend on the desired effect, on the duration of treatment and on the administration route used; they are generally from 1 to 15 mg of sibutramine per day by the oral route for an adult and from 0.10 to 500 mg of the CB1 receptor antagonist per day by the oral route for an adult.

Generally, the doctor will determine the appropriate dosage according to the age, weight and any other factor specific to the subject to be treated.

What is claimed is:

1. A combination of a CB1 receptor antagonist and sibutramine, its hydrate or one of its pharmaceutically acceptable salts, wherein the CB1 receptor antagonist is: 1-[bis(4-chlorophenyl)methyl]-3-[(3,5-difluorophenyl)(methylsulfonyl)methylene]azetidine, or a pharmaceutically acceptable salt thereof.

2. The combination according to claim 1, wherein the components of the combination are administered simultaneously, separately or spread out over time.

3. The combination according to claim 1, wherein each component of the combination is administered in a single dose or in multiple doses.

4. A composition comprising a CB1 receptor antagonist and sibutramine, its hydrate or one of its pharmaceutically acceptable salts, wherein the CB1 receptor antagonist is: 1-[bis(4-chlorophenyl)methyl]-3-[(3,5-difluorophenyl)(methylsulfonyl)methylene]azetidine, or a pharmaceutically acceptable salt thereof and at least one compatible and pharmacologically acceptable diluent or adjuvant.

5. The composition according to claim 4, comprising 0.5 to 10 mg of sibutramine and 0.1 to 200 mg of the CB1 receptor antagonist.

6. The composition according to claim 4, further in combination with a pharmaceutically compatible and physiologically active product.

7. A process for treating obesity in a mammal, comprising administering to the mammal in need thereof an effective amount of at least one CB1 receptor antagonist and sibutramine, its hydrate or one of its pharmaceutically acceptable salts, wherein the CB1 receptor antagonist is: 1-[bis(4-chlorophenyl)methyl]-3-[(3,5-difluorophenyl)(methylsulfonyl)methylene]azetidine, or a pharmaceutically acceptable salt thereof.

8. The process for treating obesity in a mammal according to claim 7, wherein sibutramine is administered at a con

17

centration ranging from 0.5 to 10 mg and the CB1 receptor antagonist is administered at a concentration ranging from 0.1 to 200 mg.

9. The process for treating obesity in a mammal according to claim 7, wherein the CB1 receptor antagonist and sibutramine are administered simultaneously, separately or spread out over time.

18

10. The process for treating obesity in a mammal according to claim 7, wherein the CB1 receptor antagonist is administered in a single dose or in multiple doses.

11. The process for treating obesity in a mammal according to claim 7, wherein sibutramine is administered in a single dose or in multiple doses.

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